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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 14, 2011
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-406 (2^{nd} review cycle)
Applicant	Johnson & Johnson
Date of Submission	December 31, 2010
PDUFA Goal Date	July 3, 2011
Proprietary Name / Established (USAN) names	Xarelto/ rivaroxaban
Dosage forms / Strength	Oral tablets, (10 mg)
Proposed Indication(s)	for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery
Recommended:	Approval, with agreed upon revisions to sponsor's proposed labeling and post-marketing commitments as indicated

1. Introduction

Patients undergoing total hip replacement surgery or total knee replacement surgery are at increased risk for venous thromboembolic events (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). Current practice recommends anticoagulant thromboprophylaxis following these procedures. Consideration for thromboprophylaxis seeks to balance risk of VTE and risk of bleeding. Several anticoagulant drug products are currently approved and marketed in the U.S. for thromboprophylaxis in hip and/or knee replacement surgery. These include: Lovenox (enoxaparin sodium)(hip replacement and knee replacement), Arixtra (fondaparinux sodium) (hip replacement, knee replacement, and hip fracture surgery) and Fragmin (dalteparin sodium)(hip replacement). All these products are administered subcutaneously. In addition heparin sodium is labeled generally for subcutaneous administration for prophylaxis of DVT. Coumadin (warfarin sodium) administered orally is approved generally "for the prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism".

Xarelto (rivaroxaban) Tablets is an orally administered Factor Xa inhibitor being developed as an anticoagulant for several indications. Relevant IND applications include IND 64,892 (rivaroxaban, BAY 59-7939) for antithrombotic indications and (b) (4) for cardiovascular indications including stroke prevention in non-valvular atrial fibrillation and use in acute coronary syndromes. In the current NDA application the sponsor is seeking initial U.S. marketing approval of rivaroxaban for the indication: "for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery". The proposed dose is 10 mg orally once daily with a treatment duration of 14 days for knee surgery and 35 days for hip surgery. Xarelto was approved for this indication in Europe and Canada in September 2008 and has been approved in some other countries also.

If approved, rivaroxaban would be the first oral anticoagulant approved in the U.S. for the indication being sought and the second oral anticoagulant approved in the U.S. for any indication since approval of warfarin in 1954. [Pradaxa (dabigatran), an orally administered antithrombin inhibitor, was approved on October 19, 2010 in the U.S. for the indication "to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation"]. Other indications for which phase 2 or 3 clinical investigations of rivaroxaban are ongoing include: for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for thromboprophylaxis in hospitalized medically ill patients, and in patients with acute coronary syndromes (ACS). Concurrent with the current resubmission of NDA 22-406 the sponsor has submitted a separate application (NDA 202439) on January 4, 2011 (received January 6, 2011) for long-term use of rivaroxaban for the prevention of stroke and systemic embolism in patients with chronic non-valvular atrial fibrillation. That application is currently under review by the Division of Cardiovascular and Renal Products (DCRP).

2. Background

This is the second review cycle for this drug product. See my Medical Team Leader/CDTL review dated 5/27/2009 for background and summary of cycle 1 review findings. Briefly, the database consisted of four trials (the RECORD 1, 2, 3, and 4 studies), each comparing rivaroxaban to enoxaparin (different regimens) with two studies for knee surgery and two studies for hip surgery. All four studies were multinational, randomized (1:1), double-blind, double-dummy, active control (enoxaparin), parallel groups design. The studies were conducted by Bayer but the right of reference for use of the studies was transferred to Johnson & Johnson (J & J) just prior to NDA submission and J & J is the sponsor of the NDA. The efficacy findings of the first cycle review found statistically significant evidence for efficacy in all 4 studies with incidence rates for the primary efficacy endpoint ("total VTE") for the rivaroxaban and enoxaparin arms, respectively, in the studies as follows: 1.1% (18/1595) and 3.7% (58/1558) in RECORD 1; 2.0% (17/864) and 9.3% (81/869) in RECORD 2; 9.6% (79/824) and 18.9% (166/878) in RECORD 3; and 6.9% (67/965) and 10.1% (97/959) in RECORD 4. A meeting of the Cardiovascular and Renal Drugs Advisory Committee on March 19, 2009 concluded that favorable benefit-risk profile had been demonstrated for use of rivaroxaban in the prophylaxis of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery, but voiced some concerns about the strength of the signals for hepatotoxicity and the feasibility of long-term studies to further elucidate the hepatotoxicity potential. Subsequent to the advisory committee meeting, findings of the Division of Scientific Investigations (DSI) inspections of several sites, particularly in RECORD 4, identified deficiencies with regard to compliance with study procedures, completeness in reporting of adverse events and other irregularities during the conduct of the RECORD studies raising questions about the adequacy of study monitoring by Bayer and necessitating further examination of the integrity of the studies by DSI.

On May 27, 2010 the Agency issued a Complete Response (CR) letter to Johnson & Johnson (Appendix B) citing results from the DSI clinical investigator inspections indicating that some sites may be unreliable and results from the sponsor (Bayer) inspection revealing that "the sponsor failed to 1)ensure proper monitoring of the study, 2)to ensure that study was conducted in accordance with the protocol and/or investigational plan, and 3)to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks." The sponsor was requested to provide a detailed report of their clinical quality assurance (QA) audit plan including plan for securing investigator compliance, audit findings, corrective actions including termination of investigators, oversight of CROs and Bayer handling of review information obtained from the CROs. The sponsor was asked to plan and perform an additional audit and provide a full report.

Also, in the CR letter the sponsor was informed that the supplied clinical data were insufficient to fully characterize a potential risk for serious liver toxicity. The sponsor was asked to provide additional long-term safety data from the studies of rivaroxaban in patients with atrial fibrillation (ROCKET srtudies), post-marketing experience outside the U.S., final reports for other completed long-term treatment studies and summary of post-marketing studies initiated outside the U.S.

Finallly, the CR letter included deficiencies identified by Chemistry, Manufacturing and Controls (CMC) review including problems with dissolution specifications, inadequate information about the drug substance, significant DMF deficiencies and issues regarding the proposed labels.

In the resubmission the sponsor has provided a full response to the CR letter.

3. CMC/Device

The product is an immediate release 10 mg tablet. During this review cycle upon recommendation by ONDQA Biopharmaceutics review (Tapash K. Ghosh, Ph.D., 3/23/2011) the sponsor revised the dissolution specifications and method adequately (see review by Tapash K. Ghosh, Ph.D., 5/2/2011). The CMC review completed by Joyce Z. Crich, Ph.D. (signed 6/2/2011) found the additional submitted materials and response acceptable from a CMC standpoint and recommended approval of Xarelto with a 30 month shelf life for the drug product in HDPE bottles and a 18 month shelf life for the drug product in blisters, when stored under specified conditions. The Office of Compliance has given an overall acceptable recommendation for the facilities and from a CMC standpoint, this NDA is recommended for approval (CMC Review #3, Janice Brown, Ph.D., 6/14/2011). There were no recommendations for Phase 4 commitments or risk management measures.

4. Nonclinical Pharmacology/Toxicology

The application was found acceptable for approval from a Non-clinical Pharmacology/Toxicology viewpoint during the first cycle. No new non-clinical data are provided in the CR submission for NDA 22-406. However, the sponsor has provided full reports of carcinogenicity studies in the NDA 202-439 application for long-term use of rivaroxaban in patients with atrial fibrillation. The non-clinical carcinogenicity studies are not required for approval of the drug for the short-term thromboprophylaxis use proposed in NDA 20-406. However, review of those studies has been completed (Patricia P. Harlow, Ph.D., 06/13/2011). Two year carcinogenicity studies were performed in CD-1 mice and Wistar rats. The review found no significant evidence of neoplasia related to rivaroxaban in either rats or mice. The Executive Carcinogenicity Assessment Committee also concluded that there were no clear drug-related neoplasms in either study. The review concluded that the results of the carcinogencity studies support approvability of rivaroxaban. Dr. Harlow's review also provided recommendations for section 13.1 of the labeling based on the results of the carcinogenicity studies.

5. Clinical Pharmacology/Biopharmaceutics

Though no Clinical Pharmacology deficiencies precluding approval were included in the CR letter, the letter did request that the sponsor provide a description of its plans to develop a lower strength formulation to be used for dose modification in certain special populations. The sponsor's response included a study synopsis and proposal to conduct a Phase 1 drug

interaction study (RIVAROXACS1001) in patients with mild or moderate renal impairment concomitantly receiving erythromycin, a moderate CYP3A4/moderate P-gp inhibitor. The FDA Clinical Pharmacology Review (Joseph Grillo, Pharm.D., 6/3/2011) agreed with the sponsor's planned study. For other populations the sponsor's submission provided discussion regarding the sponsor's belief that a lower dose formulation was not needed for patients with Child Pugh class B patients without coagulopathy or for patients concurrently receiving Xarelto and a P-gp and strong CYP3A4 inhibitors. FDA Clinical Pharmacology was not persuaded by the sponsor's arguments and the Dr. Grillo's review of the resubmission concluded: "From a clinical pharmacology perspective, this resubmission of the original application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with rivaroxaban treatment." The following were listed as post-marketing commitments: (1)Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement, and (2)evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation. Also, the review recommended that the sponsor evaluate the effect of a P-gp inhibitor with limited CYP3A4 inhibitory activity (e.g., quinidine) on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in healthy subjects to explore the involvement of P-gp in rivaroxaban elimination.

The Clinical Pharmacology review provided detailed recommendations for the labeling. It also recommended that, until the sponsor has developed a lower dose formulation for use in patients with Child Pugh class B hepatic impairment without coagulopathy and in patients with concurrent rivaroxaban use with a P-gp and strong CYP3A4 inhibitor, avoidance language should be included in the labeling for these populations.

6. Clinical Microbiology

The product is an oral formulation. No clinical microbiology information was submitted for this application.

7. Clinical/Statistical- Efficacy

This is the second review cycle for this supplemental application. During the first review cycle Clinical Review (Min Lu, M.D., M.P.H., signed 4/2/2009) concluded that efficacy of rivaroxaban had been demonstrated. The review stated: "Overall, rivaroxaban demonstrates efficacy in prophylaxis of total VTE in patients undergoing elective hip or knee replacement

surgeries. The absolute risk reduction of rivaroxaban for total VTE was 2.6% for total hip replacement surgery (RECORD 1 study), and 3.2% for total knee replacement surgery (RECORD 4 study) compared to currently available product (enoxaparin) with the similar treatment duration. The difference between the two treatments was mostly due to asymptomatic DVT. These results were based on 67% of all randomized population. There was no significant difference for the symptomatic VTE between the two treatments in these two studies based on 97% of randomized population." Statistics Review (Qing Xu, Ph.D., 5/8/2009) of the original application during the first review cycle found, "Statistical analysis results, based on the data of the 4 pivotal studies, demonstrate the drug efficacy using Rivaroxaban in the treatment of major VTE when compared with Enoxaparin control. Findings from using different approaches to deal with missing data issues with the primary endpoint consistently concluded the robustness of the primary efficacy results." After completion of the reviews, information from Division of Scientific Investigations (DSI) inspections of sites in the RECORD studies, raised concerns regarding data integrity for the studies. (See section 11 below). Therefore, for the clinical review of the resubmission efficacy was re-evaluated considering the results of the more extensive auditing of the studies that was conducted in response to the CR letter.

DSI review of the resubmission concluded that RECORD 4 was unreliable and the data should not be used. (Susan D. Thompson, M.D., 5/25/2011). This leaves the RECORD 1 and 2 studies for thromboprophylaxis in total hip replacement and a single study RECORD 3 for thromboprophylaxis in total knee replacement. For each of these three studies, one or more audited sites also were found to be unreliable. FDA Statistics conducted analysis by excluding all unreliable sites for RECORD 1, 2, and 3 identified by DSI; and the results did not alter the original efficacy conclusion (Qing Xu, Ph.D., final signature 5/27/2011). In her current Clinical Review (signed 6/3/2011) of the resubmission Dr. Lu states, "Rivaroxaban has been shown to reduce the rate of total venous thromboembolic events (VTE) inpatients undergoing hip or knee replacement surgery as compared to the control (enoxaparin or enoxaparin followed by placebo)." Secondary clinical review (Kathy Robie Suh, M.D.,Ph.D., 6/13/2011) after considering the impact of the unreliable sites concludes that, "With regard to efficacy, overall, the results support that rivaroxaban is effective in reducing VTE events in patients undergoing hip or knee surgery. However, considering the shortcoming in the monitoring adequacy in the studies, quantitative expression of that effectiveness as compared to the enoxaparin comparator in these studies may not be reliable. I would not conclude superiority of rivaroxaban over enoxaparin for the indication based on the results of these studies."

8. Safety

The major clinical safety concerns identified during the first cycle review were bleeding (increased risk for major bleeding) and possible hepatotoxicity. (See Clinical Review by Min Lu, M.D., M.P.H., signed 4/2/2009; Medical Team Leader/CDTL review by Kathy Robie Suh, M.D., Ph.D., dated 5/27/2009; Statistical Review and Evaluation of the clinical studies for possible liver toxicity by Chava Zibman, Ph.D., 2/26/2009; and Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) review by Kate Gelperin, M.D., M.P.H., 2/13/2009). Dr. Lu's Clincal Review mentioned limitations of short-term studies for

evaluation of safety and recommended that, "Additional safety data of rivaroxaban from ongoing ROCKET-AF studies and recently completed trial of ATLAS ACS TIMI 46 6-months trial should be submitted for evaluation of the risk for hepatotoxicity to allow assessment of benefit and risk of rivaroxaban for the proposed indication." Dr. Zibman's Statistical Review and Evaluation of the clinical studies for possible liver toxicity during the first cycle commented, based on the aggregate data from the RECORD studies, "In summary, according to the data evaluated in this memorandum, it might be difficult to differentiate between Rivaroxaban and Enoxaparin patients based on signals of liver toxicity in the data. In fact, a smaller proportion of Rivaroxaban patients than Enoxaparin patients have elevated enzyme or TBL levels or experience hepatobiliary adverse events." Dr. Gelperin's review concluded, "A potential signal for severe liver injury associated with rivaroxaban therapy has not been fully characterized at this time. Complete risk assessment, fully evaluating safety data from long term clinical trials, should be undertaken in order to inform decisions about the balance of therapeutic benefit versus risk with rivaroxaban."

In the resubmission long-term safety data from the completed studies of rivaroxaban in non-valvular atrial fibrillation and other long-term studies were reviewed.

Statistical Review of the safety data for evaluation of potential hepatotoxicity was done by John Yap, Ph.D. (6/10/2011). The review assessed liver toxicity based on the results of five trials of rivaroxaban at dose of 10-30 mg daily for chronic use (>35 days and up to 4 years) for stroke prevention in patients with atrial fibrillation (ROCKET and J-ROCKET studies), and for treatment in patients with deep venous thrombosis (EINSTEIN-DVT study or pulmonary embolism (EINSTEIN-PE) and extended DVT/PE treatment (EINSTEIN Extension study). The proportions of patients with elevated alanine aminotransferase (ALT) at predefined multiples of the upper limit of normal (ULN) were generally balanced between the rivaroxaban and warfarin arms in the atrial fibrillation trials and were lower in some cases in the rivaroxaban arm as compared to the enoxaparin arm in the VTE studies. Occurrence of "Hy's Law cases" (concurrent values of ALT>3x ULN and total bilirubin >2x ULN) in the atrial fibrillation studies was similar in the rivaroxaban (0.45%; 34/7618) and warfarin (0.47%; 36/7650) arms. In the DVT/PE treatment studies overall Hy's Law cases were 0.17% (6/3560) with rivaroxaban ttreatment and 0.17% (6/3487) with enoxaparin. In the DVT extended treatment study there were no Hy's Law cases. The review states,

> "In conclusion, findings from this review suggest that the liver toxicity profile based on assessment of evaluated ALT, TBL [total bilirubin], and of reported hepatic events, of rivaroxaban is comparable to active controls, warfarin and enoxaparin, studied across four randomized clinical trials. No notable differences in these outcomes were identified in a single placebo-controlled trial versus rivaroxaban. Lastly, the incidence of Hy's Law cases were similar between the rivaroxaban and warfarin arms in the Rocket trials; however, these events occurred earlier (within the first year) in the warfarin arm compared to the rivaroxaban arm."

The review noted, however, that the dose (10 mg/daily) and duration (up to 35 days) of rivaroxaban studied in the RECORD 1-4 trials was lower and shorter, respectively, compared to the dose and duration of rivaroxaban studied in the ROCKET and EINSTEIN studies.

Rivaroxaban is approved in Canada and the European Union (September 2008) for prophylaxis of VTE in patients undergoing hip or knee replacement surgery and is also approved in some other countries. Post-marketing safety information and safety information from an observational post-marketing safety study were included in the resubmission. The most common serious adverse events reported were bleeding events. Other serious adverse events in the reports were cerebral hemorrhage (9 cases, 3 deaths), agranulocytosis (3 cases; 1 death), hypersensitivity reactions (3 cases; no deaths) anaphylactic shock (2 cases; no deaths); anaphylactic reaction (2 cases; no deaths); Stevens-Johnson syndrome (2 cases; no deaths). (See Dr. Min Lu's Clincal Review, completed 6/3/2011 for details).

Dr. Lu's Clincal Review states, "The overall benefit of rivaroxaban treatment is considered to outweigh the risk for the proposed use in the intended population."

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this resubmission.

10. Pediatrics

No pediatric information is included in this resubmission. See the first review cycle Medical Team Leader Secondary Review/CDTL Review by Kathy Robie Suh, signed 5/27/2009 for a summary of comments from the Pediatric group of the Maternal and Pediatric Health Team (PMHS) regarding the potential for use of rivaroxaban in pediatric patients. For this resubmission the PMHS was consulted to provide comments and recommendations for labeling regarding use in pediatric patients and use in pregnant women and nursing mothers. Pediatric Review of the resubmission for proposed pediatric labeling (Elizabeth Durmowicz, M.D., 6/10/2011) agreed with a full waiver of PREA studies for this application since studies would be impossible or highly impractical because there are too few children with the disease/condition, i.e. pediatric patients undergoing hip or knee replacement surgery. Because studies have not been conducted in pediatric patients and no specific pediatric safety concerns have been identified, the review agreed that the statement, "Safety and effectiveness in pediatric patients have not been established" should be included under the Pediatric Use section of the label.

Also, the Maternal Health Team provided review and recommendations for wording in the labeling regarding use and risks for the use of rivaroxaban in pregnancy and nursing mothers. The review (Bhatnagar Upasana, M.D., 6/10/2011) recommended Pregnancy Class C designation for the drug, indicating that studies have not been conducted in pregnant women but commenting that preliminary results suggest that animal reproduction studies show no increased risk of structural malformations but an increased risk of post-implantation pregnancy loss in rabbits. The review voiced concern about the risk for obstetric-related bleeding and possible emergent delivery and noted the lack of an antidote for rivaroxaban and no monitoring for degree of anticoagulation. The review recommended language for warnings and precautions in the labeling regarding these risks. For nursing mothers the review recommended that the labeling indicate that it is not known if rivaroxaban or its metabolites in found in human milk but that it appears in rat milk. The review commented that because of

the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Women of childbearing potential who require anticoagulation should discuss pregnancy planning with their physician.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations (DSI) review of the resubmission (Susan D. Thompson, 5/25/2011) provided a thorough evaluation of the data and materials submitted in response to the concerns regarding the quality of monitoring and oversight for the RECORD studies. The resubmission included audit information from inspections of 4.9% (30/619) sites and encompassing 7.4% (945/12729) of patients. The review found one or more of the audited sites within each of the RECORD studies to be unreliable. These included three sites in RECORD 1 (Lenart, Porvaneckas, and Slappendel), four sites in RECORD 2 (Corces, Yang, Naraffete, Ono) and one site in RECORD 3 (Brabants). For RECORD 4 the review found that deficiencies in the audited sites were sufficiently severe and pervasive as to render the entire study unreliable. The review summarized the findings as follows:

> " In summary given the pervasive findings of deficient clinical trial monitoring, high number of clinical investigator sites with data assessed as unreliable, failure to follow the protocol including postoperative randomization, and deficient clinical trial conduct including failure to report significant adverse events and SAEs, DSI cannot provide a favorable assessment of RECORD 4 data reliability for the remaining unaudited sites based on extrapolation of the Falcon audit findings. Although some issues exist with the study conduct of RECORD 1, 2, and 3, they are not sufficiently pervasive to recommend an unfavorable assessment of data reliability. Therefore, the data from RECORD 1, 2, and 3, with exception of select sites as identified earlier, are considered reliable in support of the application. The data from RECORD 4 are not considered reliable in support of the respective indication."

The impact of the DSI review findings on the clinical assessment of the application are discussed in more detail in the Clinical Review by Min Lu, M.D., 6/3/2011 and in my Medical Team Leader Secondary Review (6/13/2011). Efficacy and safety results excluding the RECORD 1, 2, and 3 sites found to be unreliable appeared similar to the overall results for the studies.

Division of Medication Error Prevention and Analysis (DMEPA) evaluation of the proposed proprietary name Xarelto did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of the review (Denise V. Baugh, PharmD., 5/12/2011).

12. Labeling

The sponsor included proposed labeling in the resubmission. Exact wording for the labeling is being developed by the review team incorporating the recommendations from each of the review disciplines and consulting review divisions.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) (J. Dvorsky, 6/8/2011) provided comments and recommendations on the draft Package Insert for Xarelto.

13. Recommendations/Risk Benefit Assessment

The sponsor has provided adequate demonstration of efficacy and an acceptable benefit/risk profile for rivaroxaban for the desired indication. Based on review of the resubmission of this NDA, the application is acceptable for approval for the indication prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients undergoing knee replacement surgery, with labeling as discussed and agreed upon internally assuming successful negotiation with the sponsor.

The approval should include requirements for post-marketing commitments as recommended by Clinical Pharmacology (section 5 above). Also, consideration should be given to focused post-marketing surveillance for the serious adverse events of agranulocytosis and Stevens-Johnson syndrome.

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/s/

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06/14/2011